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Total Synthesis of Merrilactone A

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Merrilactone A (**1**, Figure 1), which was isolated from *Illicium merrillianum* in 2000,[1] has been shown to possess neurotrophic activity in cultures of fetal rat cortical neurons and therefore is expected to hold therapeutic potential in the treatment of neurodegeneration associated with Alzheimer's and Parkinson's diseases.[2] Apart from the biological aspects, the caged pentacyclic skeleton of **1** served to pose interesting synthetic challenges. To date, the sole synthesis of (±)-**1** was reported by Danishefsky and Birman.[3,4] Herein, we report the total synthesis of (±)-**1** employing an efficient and flexible strategy.

The construction of the *cis*-bicyclo[3.3.0]octane framework embedded within **1** was envisioned to involve the desymmetrization of *meso*-diketone **3** through an intramolecular aldol reaction (**3** → **2**, Figure 1).[5,6] This reaction would establish the relative stereochemistry of three stereocenters (C4, C5, C6) of **1**, and the asymmetric version would afford the enantiomeric **2** through a simple, single-step process. Moreover, it is practically important that **3** is efficiently prepared through pairwise symmetrical functionalizations.[7]

To begin the synthesis of **3**, [2+2] photocycloaddition between **4** and **5** was carried out to install the consecutive C5−C6 quaternary carbons to give **6** (Scheme 1).[8] Reductive dechlorination of **6** and LAH-reduction of the anhydride yielded *meso*-diol **7**, which was protected as the benzyl ethers, and then subjected to dihydroxylation to afford **8**. The Swern oxidation/allylation sequence (**8** → **9** → **10**) was performed as a one-pot reaction,[9] because of the strong tendency of diketone **9** toward hydration in the aqueous workup. In this reaction, the *cis*-introduction of allyl groups from the α-face was strongly favored to provide **10αα** as the major isomer. *cis*-Arrangement of the olefins effectively facilitated the ring-closing metathesis reaction[10] of **10** to produce bicyclo[4.2.0]octyl system **11**, which was treated with $Pb(OAc)_4$ in situ[11] to yield the eight-membered ring **3**.

The next stage of the synthesis involved the crucial transannular aldol reaction. Gratifyingly, treatment of **3** with $LiN(TMS)_2$ in THF at −100 °C led to the selective formation of desired product **2** (Scheme 1, entry 1). The influence on the selectivity by the reaction temperature (entry 2) suggested the kinetic nature of product **2** under these conditions. Interestingly, both $MgBrN(TMS)_2$ (entry 3) and $LiN(TMS)_2/Et_3N$[12] (entry 4) induced the opposite selectivity, favoring the undesired diastereomer **12**, whereas DBU did not exhibit a preference for either product (entry 5). Although the factors controlling the selectivities are yet to be clarified, we have demonstrated desymmetrization protocols that are capable of generating either diastereomer **2** or **12** by simply changing the reaction conditions.

We then turned our attention to the introduction of the C9-quaternary center and C15-methylene group (Scheme 2). Epoxidation of **2** produced α-epoxide **13**, which was converted to **15** via a two-step procedure that involved the epoxide ring opening with DBU, and then IBX oxidation.[13] An α-bromoacetal was then appended to **15** to afford **16** as a 4:1 mixture of diastereomers.

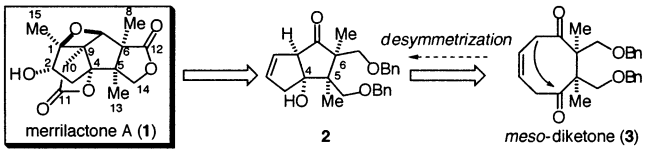
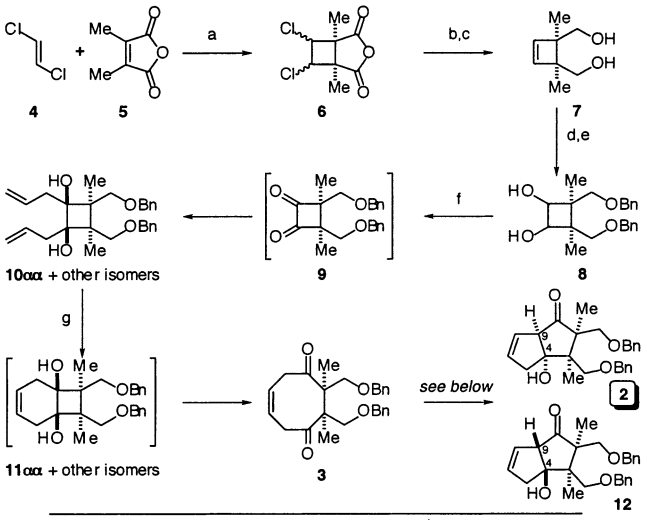


Figure 1. Retrosynthesis of merrilactone A.

Scheme 1 [a]



entry	reagents and conditions	ratio[a] 2	ratio[a] 12	combined yield
1	$LiN(TMS)_2$, THF, −100 °C	3.1	1.0	85%
2	$LiN(TMS)_2$, THF, −40 °C	2.6	1.0	78%
3	$MgBrN(TMS)_2$, Et_2O, RT	1.0	3.0	81%
4	$LiN(TMS)_2$, Et_3N, toluene, −78 °C	1.0	5.1	79%
5	DBU, CH_2Cl_2, 0 °C	1.1	1.0	63%

a) The ratio was determined by 500 MHz ^{1}H-NMR.

[a] Reagents and conditions: (a) benzophenone, acetone, *hν*, rt;(b) Zn, TMSCl, Ac_2O, toluene, 85 °C; (c) $LiAlH_4$, THF, rt, 47% (three steps); (d) BnBr, NaH, THF/DMF (10:1), rt, 99%; (e) OsO_4, NMO, *t*-BuOMe/*t*-BuOH/H_2O (1:1:1), rt, 94%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, then allylmagnesium bromide, −78 °C, 78% (**10αα**:**10ββ**:**10αβ** =15:2.6:1); (g) $(PCy_3)_2Cl_2Ru$=CHPh, CH_2Cl_2, reflux, then $Pb(OAc)_4$, rt, 95%.

Despite the steric congestion around C9 of **16**, radical cyclization using Bu_3SnH and BEt_3[14] delivered 5-exo cyclized product **17** (*β*:α = 3.5:1) in a high yield.[15] Using acidic ethanol, we transformed **17α** into the major C11-isomer **17*β***. The regioselective silyl enol formation from **17*β***, followed by reactions with Eschenmoser reagent and subsequently with mCPBA,[16] produced **18**, which has all of the carbons of **1** in place.

In regard to the successful total synthesis from **18**, the proper arrangement of the functional group manipulations was the most critical issue. Although the stereoselective reduction of the hindered C7-ketone was particularly troublesome, we found that the

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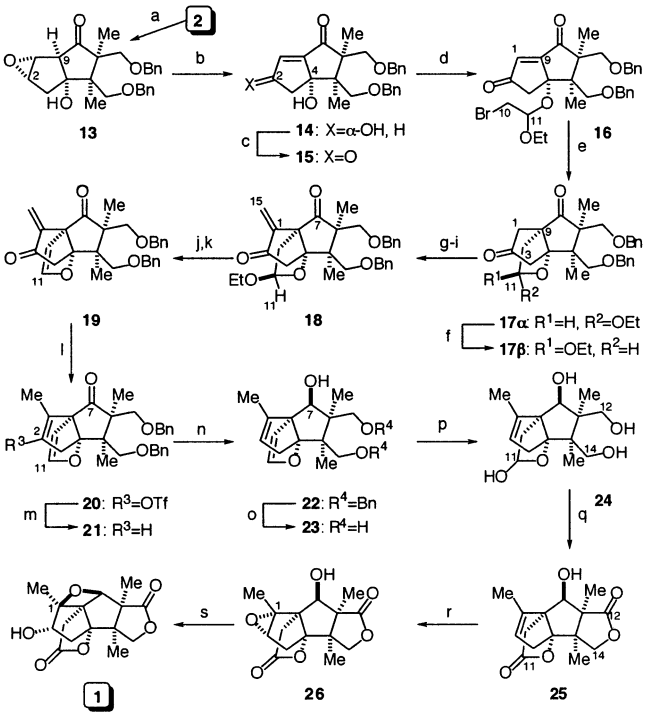
Scheme 2 [a]



[a] Reagents and conditions: (a) *m*CPBA, CH_2Cl_2, rt, 81%; (b) DBU, CH_2Cl_2, −40 °C, 81%; (c) IBX, DMSO, rt, 94%; (d) $BrCH_2Br(OEt)$, $PhNMe_2$, CH_2Cl_2, −78 °C to rt, 62% (dr = 4:1, 100% based on recovered **16**); (e) Bu_3SnH, BEt_3/O_2, toluene, rt, 57% (**17*β***), 16% (**17α**); (f) CSA, EtOH, rt, 86%; (g) TMSOTf, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, −20 °C; (h) $Me_2NCH_2{}^+I^-$, CH_2Cl_2, rt; (i) *m*CPBA, CH_2Cl_2, rt, 70% (three steps); (j) TFA/H_2O (9:1), rt, 94%; (k) MsCl, Et_3N, THF, 50 °C, 77%; (l) $LiBH(s\text{-}Bu)_3$ (L-Selectride), THF, MS4A, −78 °C then 2-Tf_2N-5-chloropyridine, −78 °C, 99%; (m) $Pd(OAc)_2$, Ph_3P, Bu_3N, HCOOH, DMF, 40 °C, 89%; (n) DIBAL, CH_2Cl_2, −78 °C, 88% (dr = 6:1); (o) Na, NH_3, THF/EtOH (5:1), −78 °C, 100%; (p) DOWEX 50WX2, THF/H_2O (2:1), rt; (q) Ag_2CO_3 on Celite, toluene, 130 °C, 64% (two steps), C14-oxidized regioisomer of **25**, 4% (two steps); (r) dimethyldioxirane, CH_2Cl_2, rt, 96%; (s) *p*-TsOH, CH_2Cl_2, rt, 81%.

stereoselectivity can be dramatically improved with the use of enol ether **21** that was synthesized as follows.[17] First, acetal **18** was transformed to enol ether **19** by a two-step sequence: (i) treatment with TFA/H_2O and (ii) mesylation and base-induced elimination. The subsequent 1,4-reduction of enone **19** using L-Selectride, followed by an in situ triflation of the resultant enolate,[18,19] generated **20**, which was then converted to olefin **21** through palladium-mediated reduction.[20] Reduction of ketone **21** using DIBAL at −78 °C in CH_2Cl_2 provided the desired isomer **22** (*β*-OH:α-OH = 6:1); presumably the enol ether contributed in reducing the steric hindrance of the hydride-accepting α-face.

Birch reduction of the benzyl ethers of **22** generated triol **23**, of which the enol ether was hydrated to give **24**. Simultaneous Fetizon oxidation[21] of the C11- and C12-alcohols in tetraol **24** proceeded with remarkable regio- and chemoselectivities to produce the desired bis-lactone **25**. Lastly, epoxidation of **25** using dimethyldioxirane[22] generated **26** as the sole product, which was subjected to acidic conditions to afford the synthetic (±)-merrilactone A (**1**) through the epoxide-opening oxetane formation.[1,3,23]

The synthesis of **1** described here should provide access to analogous structures for future biological and SAR studies. Investigations of the asymmetric desymmetrization (**3** → **2**) to prepare enantiomerically pure **1** and biological studies of the synthetic intermediates are currently underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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